Influenza prevention in human populations:
Vaccination considerations and the future of vaccines

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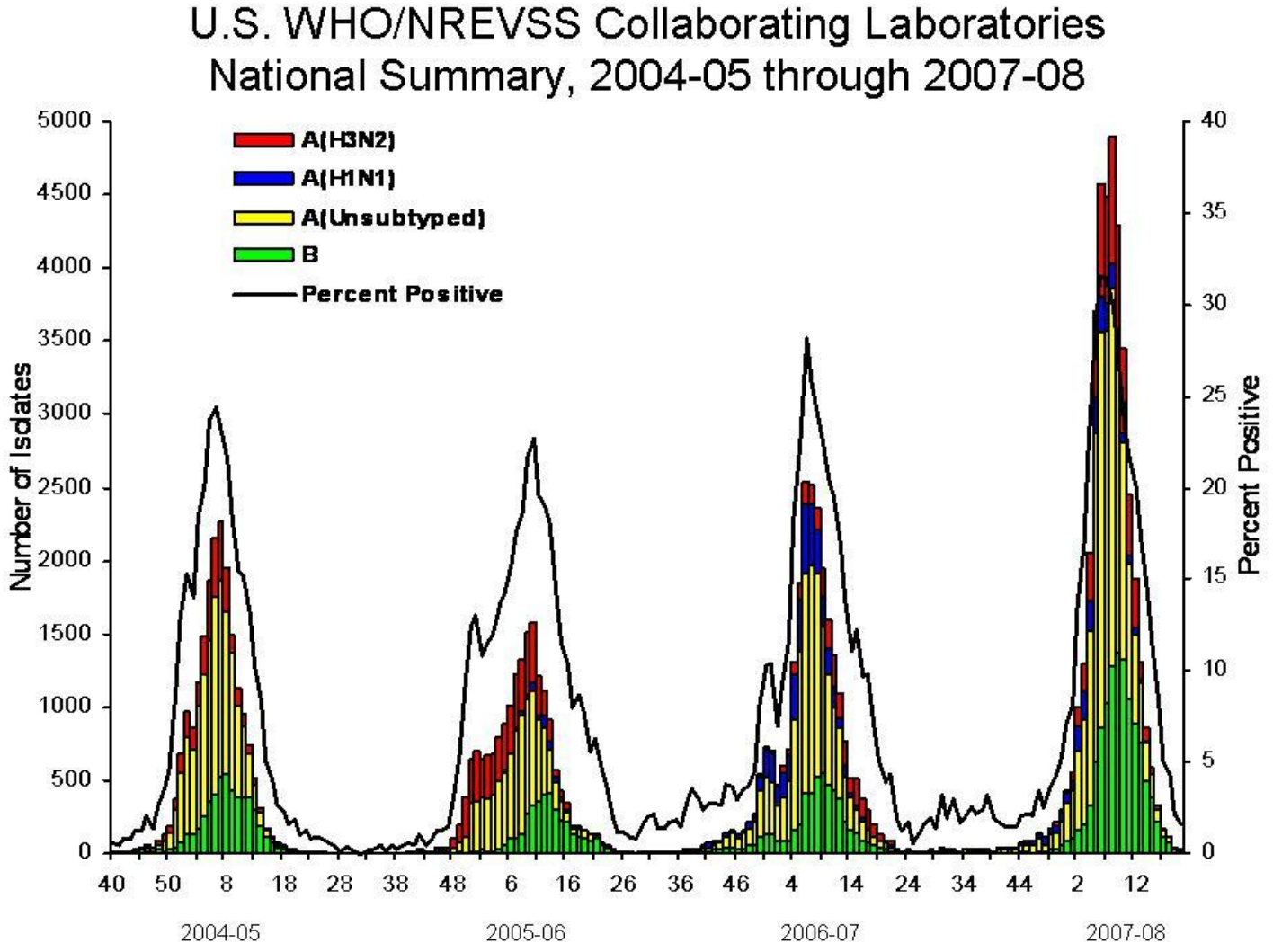
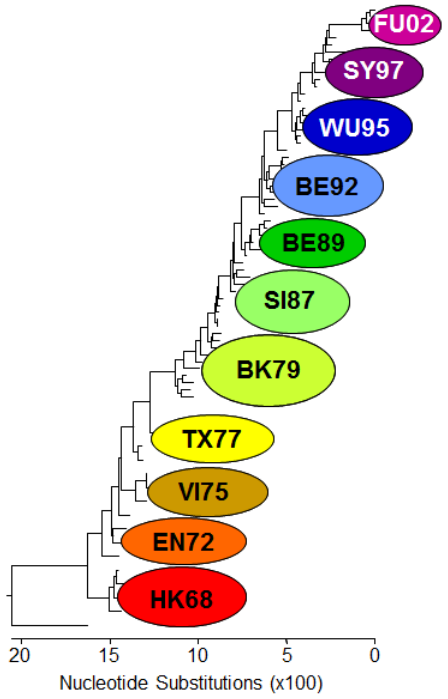
Influenza Virus: Surveillance



Reference: http://www.cdc.gov/flu/weekly/weeklyarchives2007-2008/labsummary07-08.htm

Genetic and Antigenic Comparisons



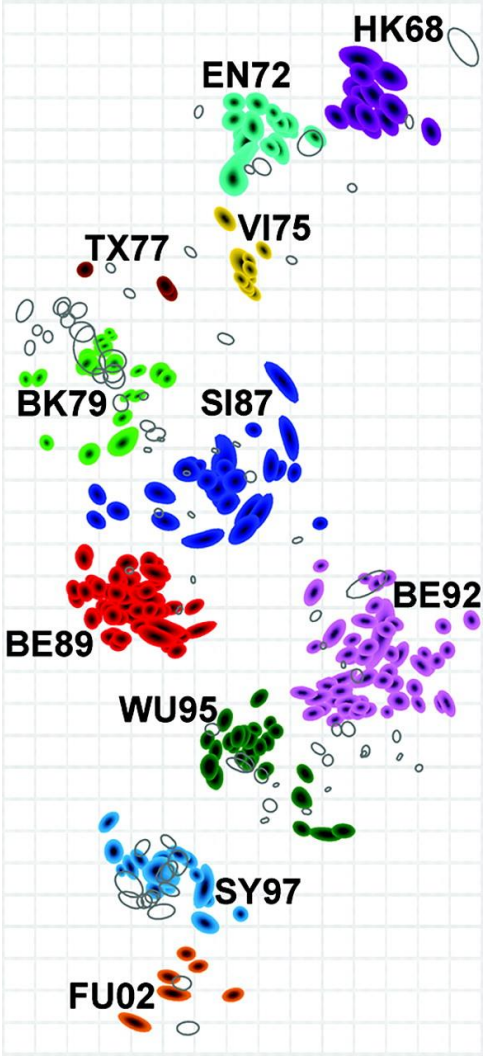
	post-infection ferret sera												
virus	A/HK 1/68	A/Eng 42/72	A/Vic 3/75	A/Tex 1/77	A/Bk 1/79	A/Phil 2/82	A/Miss 1/85	A/Shan 11/87	A/Beij 352/89	A/Beij 32/92	A/Jhb 33/94	A/Wuh 359/95	A/Syd 5/97
A/Hong Kong/1/68	**1280**	320	<	<	<	<	<	<	<	<	<	<	<
A/England/42/72	40	**640**	40	<	<	<	<	<	<	<	<	<	<
A/Victoria/3/75	<	<	**640**	<	<	<	<	<	<	<	<	<	<
A/Texas/1/77	40	40	80	**1280**	320	160	<	40	<	<	<	<	<
A/Bangkok/1/79	<	40	40	320	**1280**	160	<	80	40	<	<	<	<
A/Philippines/2/82	<	<	40	80	80	**640**	80	160	80	<	<	<	<
A/Mississippi/1/85	<	<	<	40	80	80	**1280**	160	80	<	<	<	<
A/Shanghai/11/87	<	40	<	40	80	80	40	**640**	80	<	<	<	<
A/Beijing/352/89	<	<	<	<	<	<	<	80	**2560**	<	<	<	<
A/Beijing/32/92	<	<	<	<	<	<	<	<	80	**640**	80	<	<
A/Johannesburg/33/94	<	<	<	<	<	<	<	<	40	80	**640**	80	<
A/Wuhan/359/95	<	<	<	<	<	<	<	<	<	40	40	**1280**	160
A/Sydney/5/97	<	<	<	<	<	<	<	<	<	<	<	160	**2560**

< = <40

- Both genetic and antigenic comparisons are made
- An antigenic distance of four-fold typically yields a change in vaccine isolate
- Selection is based on both antigenicity and ability to produce high-yield vaccine product

Antigenic Map of Influenza H3 Evolution in Humans

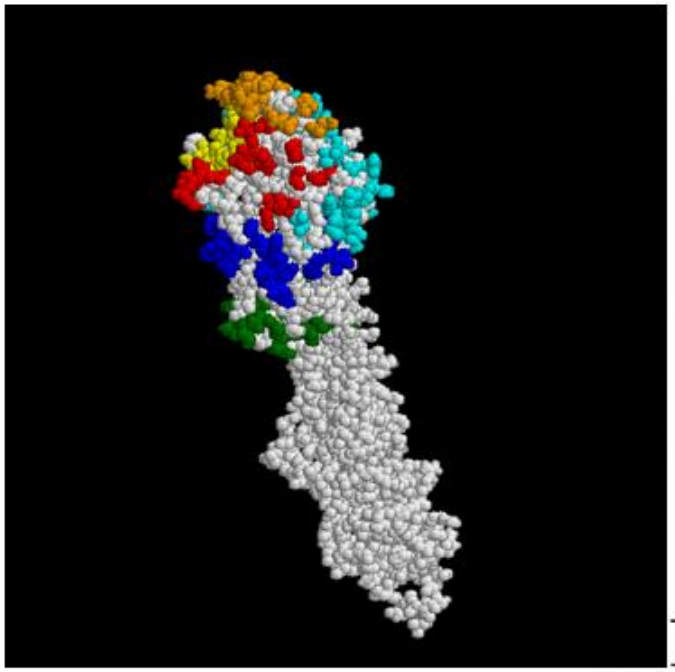
- Once influenza viruses enter the human population, they change through antigenic drift
- Clusters defined by changes in recognition of the virus by antibodies
- Vaccines are updated based on changes in circulating strains



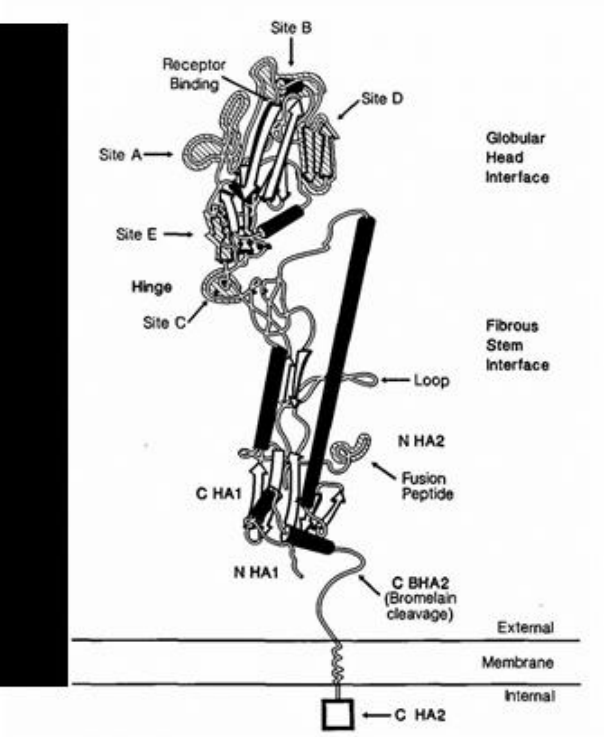
Smith et al., *Science*, **305**:371, 2004

Influenza Virus: Antigenic Sites
Antigenic Drift

Antigenic Site A
Antigenic Site B
Antigenic Site C
Antigenic Site D
Antigenic Site E
Receptor Binding



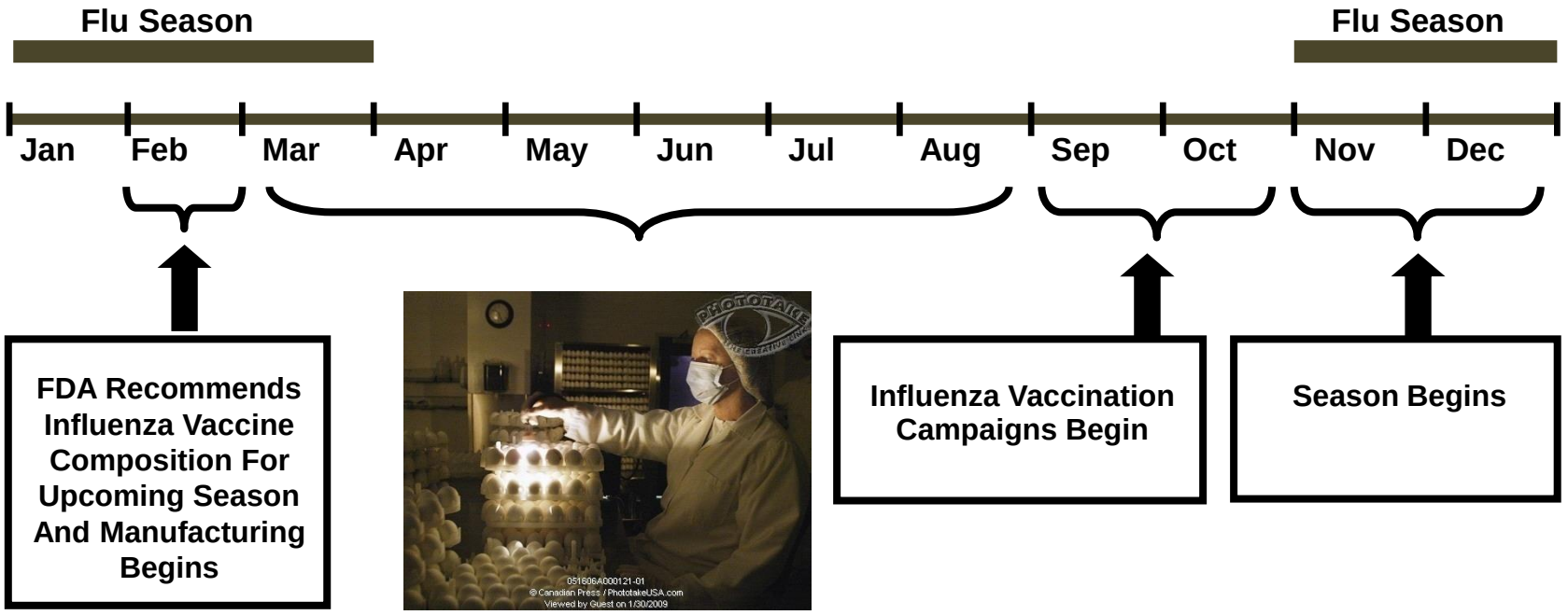
A/Hong Kong/1/68 HA



Fields Virology

- Small, continuous change:
  - Variation within the globular head

Influenza Vaccine Development Cycle (Northern Hemisphere)



Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 2006;55:1.

World Health Organization. *Wkly Epidemiol Rec*. 2002;77:229-240.

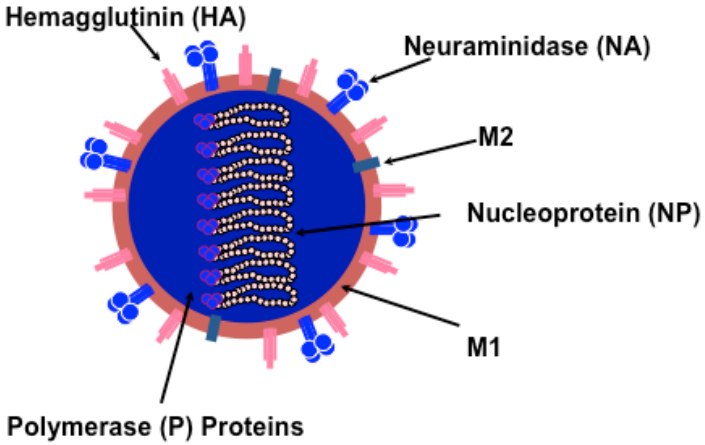
Vaccination Remains Our Best Method of Prevention Against Influenza Virus

What about anti-virals?

- Two classes of antivirals that target influenza

- M2 inhibitors (amantadine and rimantadine)
  - -resistance develops rapidly
  - -current H5N1 viruses are already resistant
  - -current H3N2 viruses are resistant (100%)

-NA inhibitors (oseltamivir and zanamivir)
  - -pre-2009 H1N1 viruses were resistant



Vaccination:
Adaptive Immunity

- Acquired Immunity
- Specificity (clearance)
- Memory develops against pathogen
    - Antibody (HA)
    - Goal of vaccination

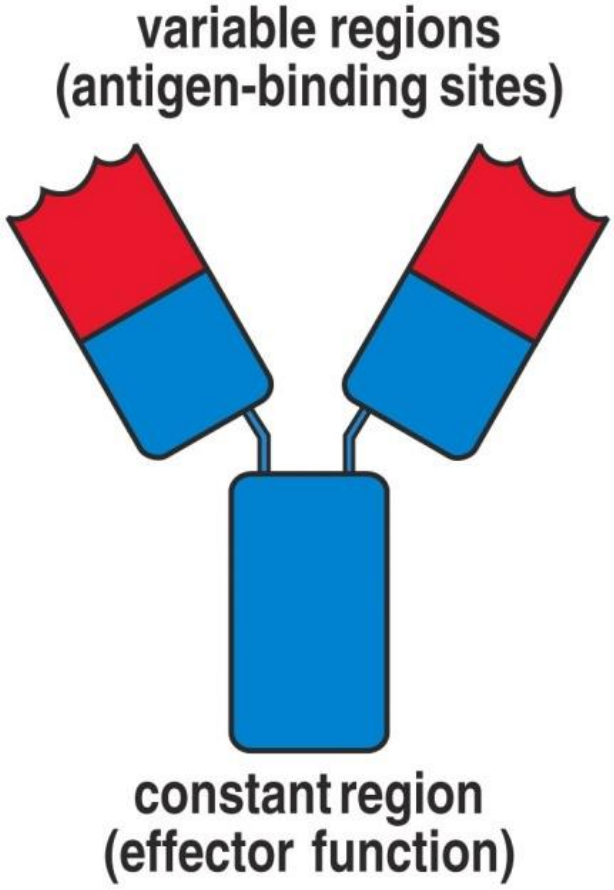


Figure 1-16 Immunobiology, 6/e. (© Garland Science 2005)

Antibody Response to Vaccination

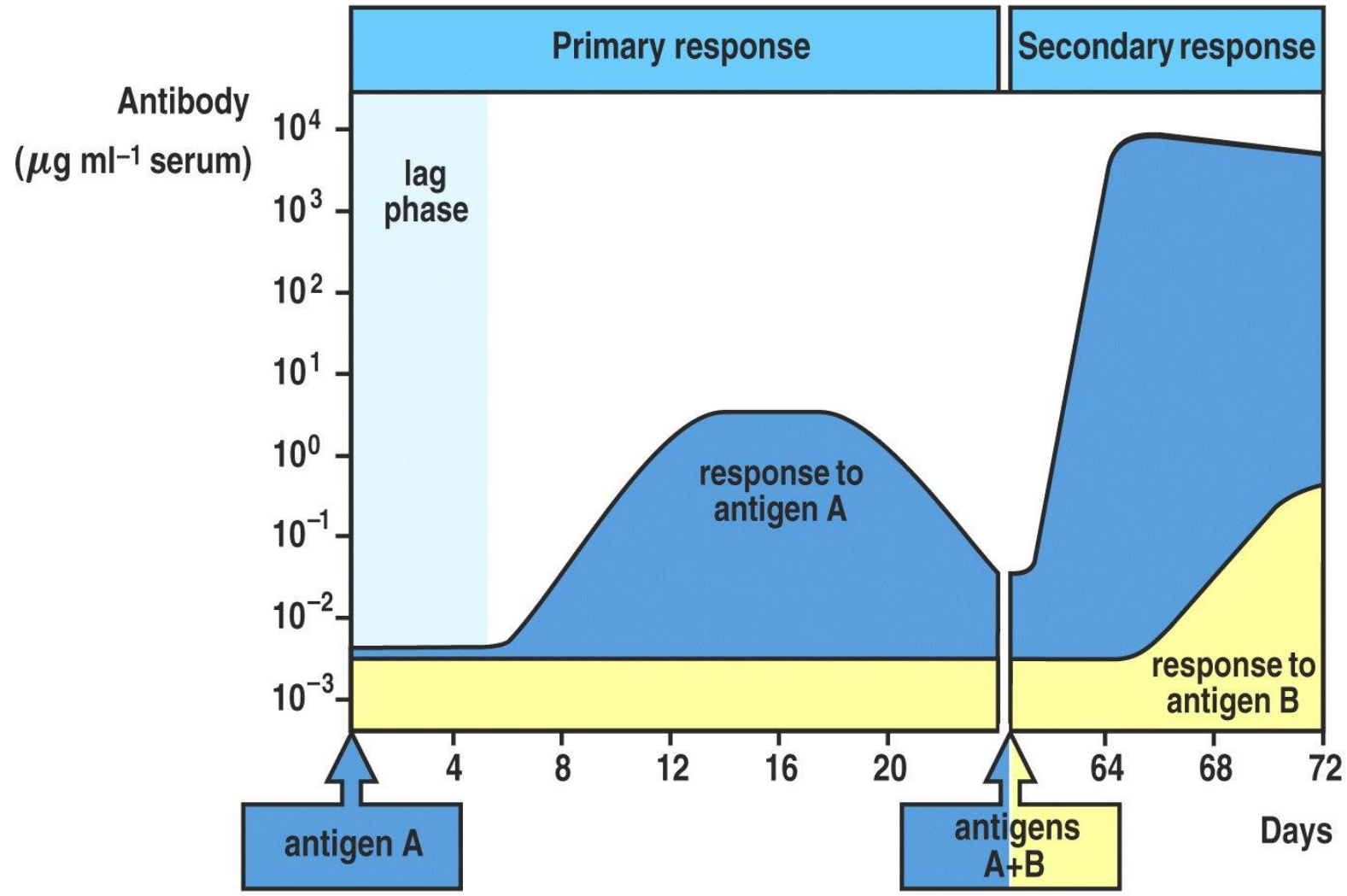
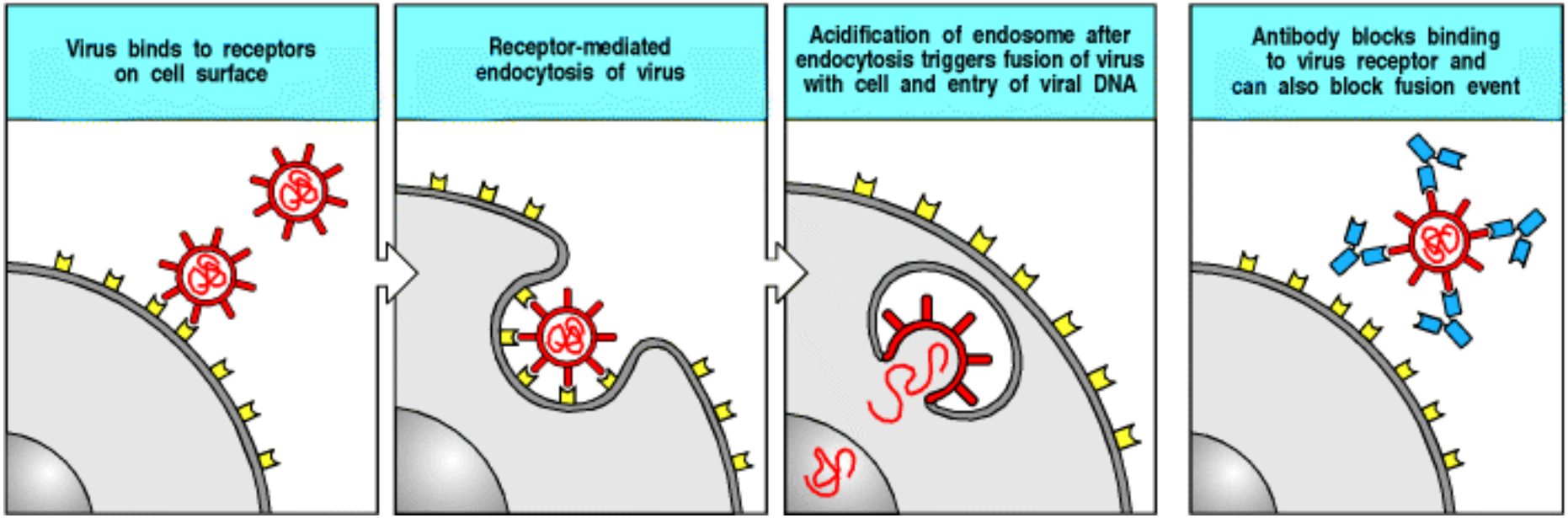


Figure 1-20 Immunobiology, 6/e. (© Garland Science 2005)

Neutralization of Viral Particles by Antibodies



Janeway *et al.*, Immunobiology, 2001

Epidemic (Seasonal) Influenza Vaccines

Trivalent or Quadrivalent vaccine H1N1, H3N2, and B viruses

Single representative isolate (determined by surveillance)

2015-16 vaccine (Northern Hemisphere): February 26, 2015

A/California/7/2009 = H1N1

A/Switzerland/9715293/2013 = H3N2

B/Phuket/3073/2013 = B (Yamagata 88 lineage)

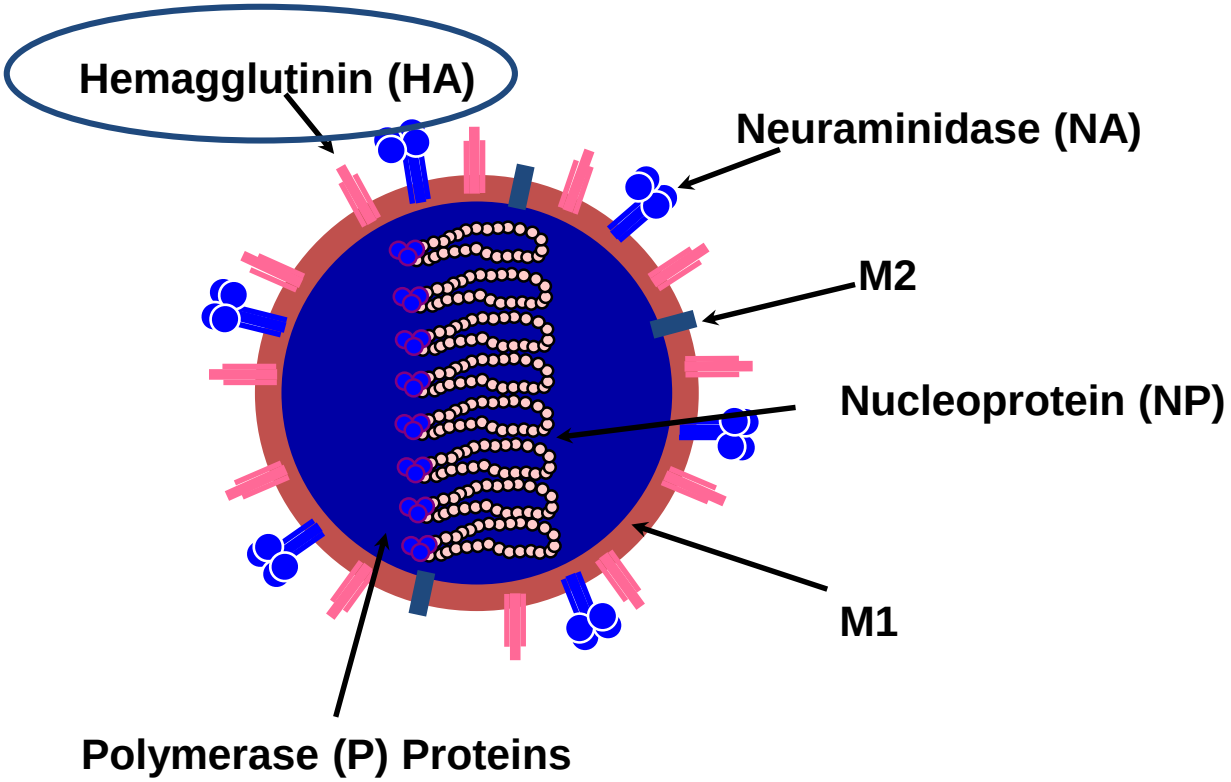
B/Brisbane/60/2008 = B (Victoria 87 lineage)

Influenza vaccines widely used in the U.S.

	Inactivated (IIV)	Live, attenuated (LAIV)
FDA-approved	Since 1960's	Since 2003
Route of administration	Intramuscular	Intranasal
Virus	Split-virus or subunit inactivated virus	Cold-adapted, temperature sensitive, live attenuated virus
Growth medium	Chicken eggs	Chicken eggs
Indication	Persons > 6 months	Healthy persons 2-49 years

Inactivated Influenza Vaccine (IIV)

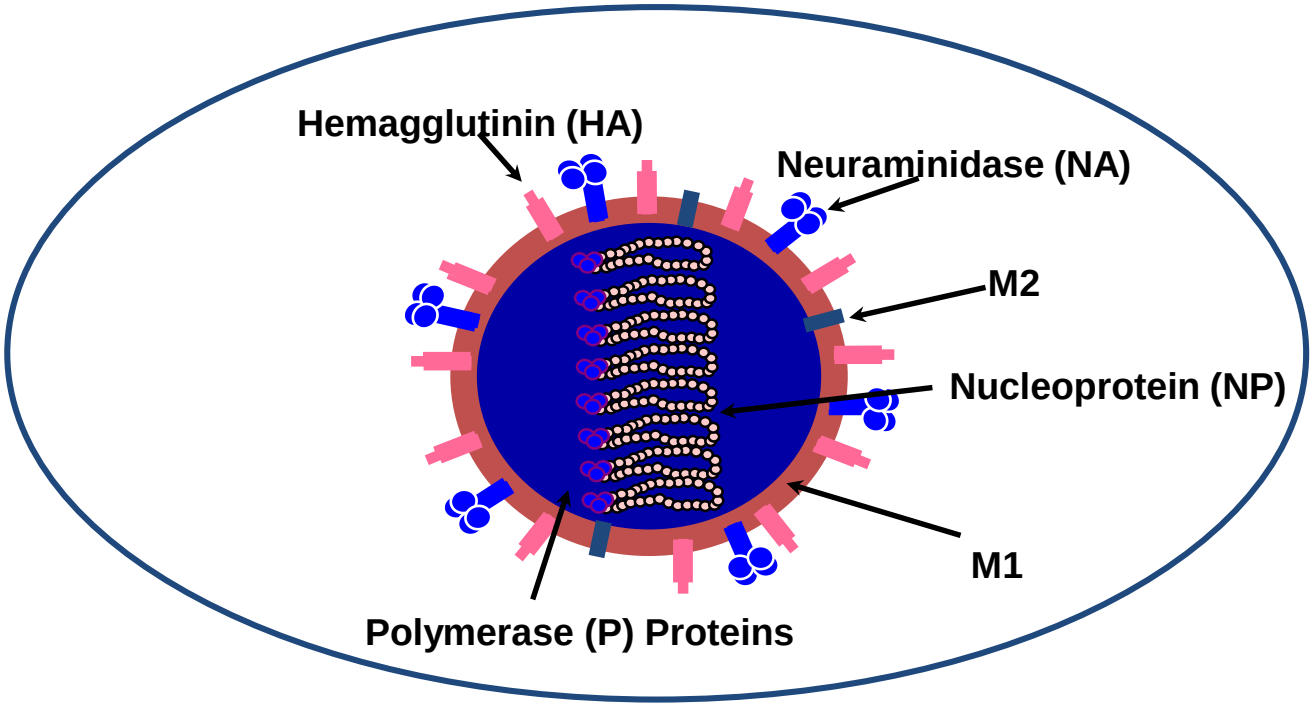
- Only hemagglutinin (HA) is included as a standardized component of IIV (15 μg HA content)



Adapted from: Hayden FG, Palese P. Clinical Virology 1997. 911-942.

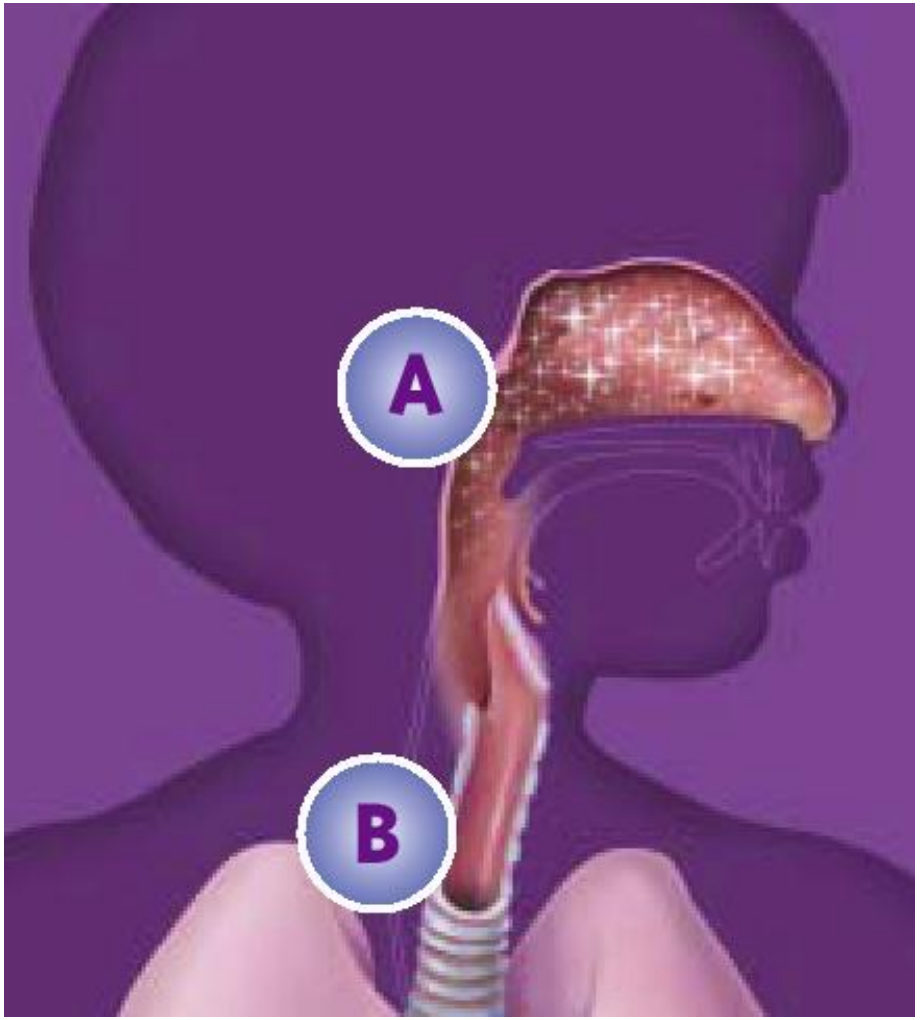
Live, Attenuated Influenza Virus (LAIV)

- Major antigens in natural configuration
- Designed to induce an immune response that resembles the response after natural infection



Adapted from: Hayden FG, Palese P. Clinical Virology 1997. 911-942.

LAIV Properties



A. Cold-adapted

- FluMist vaccine strains replicate efficiently at 25ºC
- Nasopharyngeal replication induces protective immunity

B. Temperature-sensitive

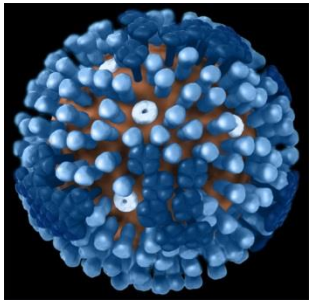
- Replication is restricted at 37ºC (Type B) or 39ºC (Type A)
- FluMist replicates inefficiently in the lower airways or lungs

FluMist™ Prescribing Information.
ACIP (Advisory Committee on Immunization Practices). *MMWR 2004 Vol. 53*.

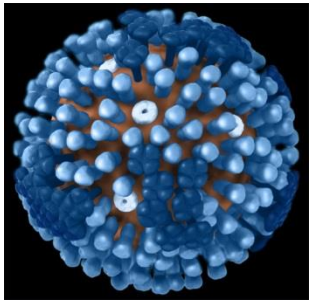
Recent Changes to Influenza Vaccines: Trivalent Vaccine Formulations

- **High dose trivalent vaccine**
  - Approved for individuals 65 and over
- **Trivalent vaccine from cell culture**
  - Approved for individuals 18 and over
- **Jet injector delivery**
  - Approved for individuals 18-64 years of age

Influenza A Virus

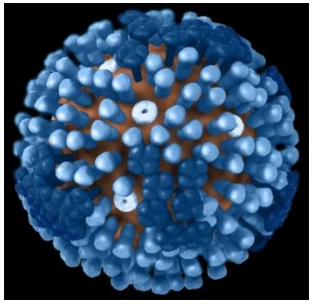


H1N1
A/California/7/2009



H3N2
A/Switzerland/9715293/2013

Influenza B Virus



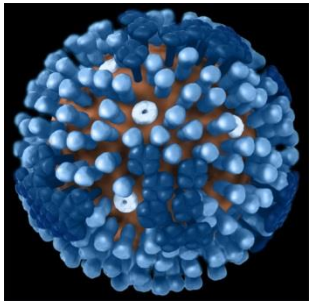
B (Yamagata lineage)
B/Phuket/3073/2013

http://www.cdc.gov/flu/keyfacts.htm, **Accessed September 10, 2015**
http://www.cidrap.umn.edu/news-perspective/2015/09/fda-panel-recommends-adjuvanted-flu-vaccine-seniors, **Accessed September 16, 2015**

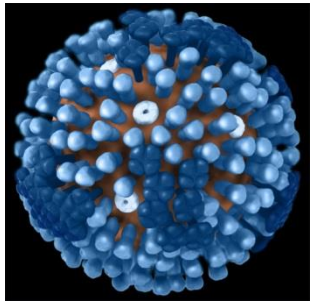
Recent Changes to Influenza Vaccines: Quadrivalent Vaccine Formulations

- **Quadrivalent vaccine (2 influenza B virus isolates)**
  - IIV: Approved for individuals as young as 6 months
  - LAIV: Approved for individuals 2-49
  - Intradermal: Approved for people 18-64

Influenza A Virus

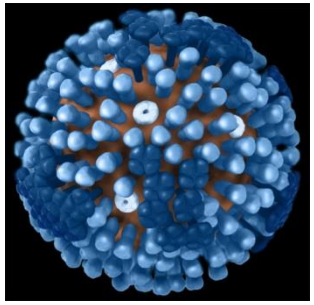


H1N1
A/California/7/2009

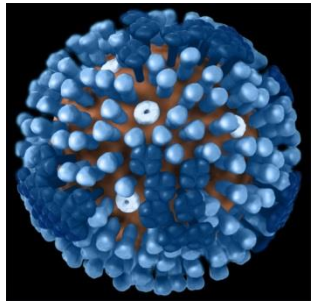


H3N2
A/Switzerland/9715293/2013

Influenza B Virus



B (Victoria lineage)
B/Brisbane/60/2008



B (Yamagata lineage)
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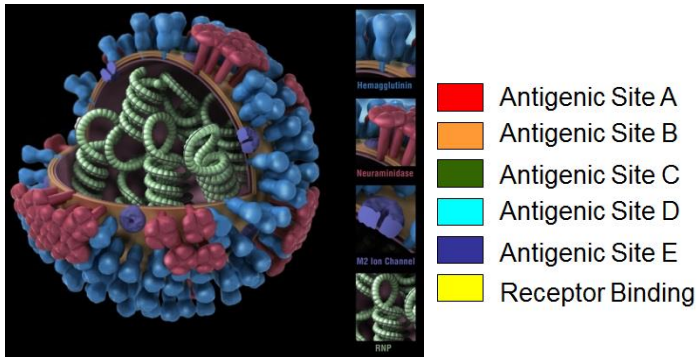
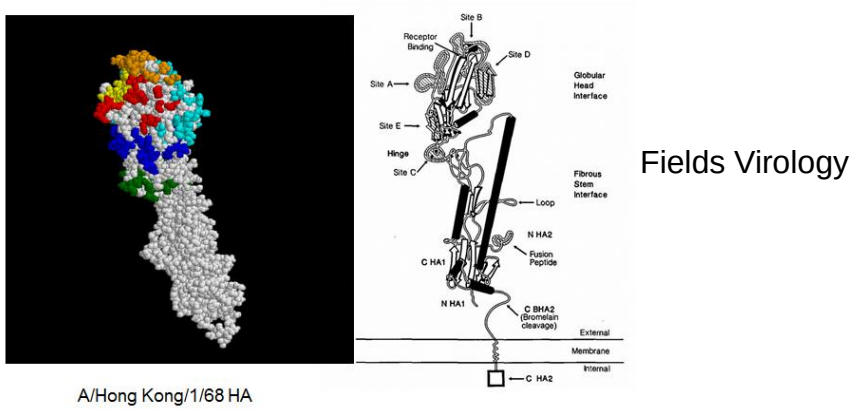
http://www.cidrap.umn.edu/news-perspective/2015/09/fda-panel-recommends-adjuvanted-flu-vaccine-seniors, **Accessed September 16, 2015**

Recent Changes to Influenza Vaccines

- **Recombinant trivalent vaccine**
  - HA protein
  - Egg-free
  - Approved for people 18 years and older (January, 2013)

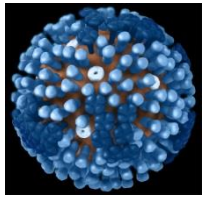




A/Hong Kong/1/68 HA

Fields Virology

- **Adjuvanted influenza vaccine**
  - MF59: Approved for use in Europe, may be approved in US soon



+ MF59

http://www.cdc.gov/flu/keyfacts.htm, **Accessed September 10, 2015**

http://www.cidrap.umn.edu/news-perspective/2015/09/fda-panel-recommends-adjuvanted-flu-vaccine-seniors, **Accessed September 16, 2015**

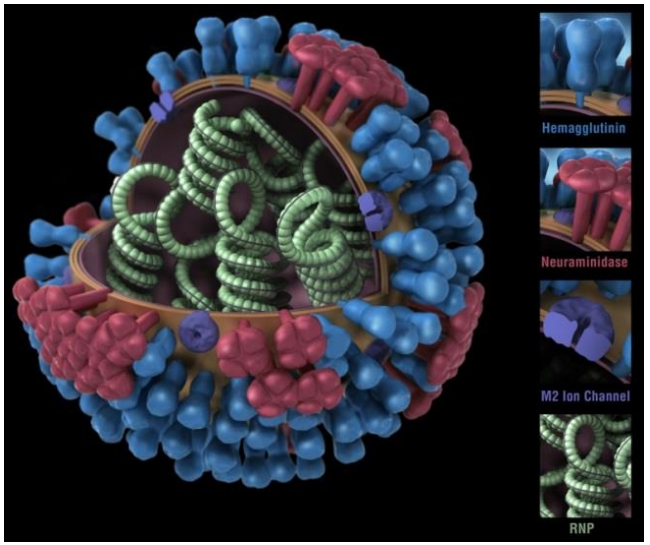
Issues Facing Influenza Vaccines

Problems with Influenza Vaccines

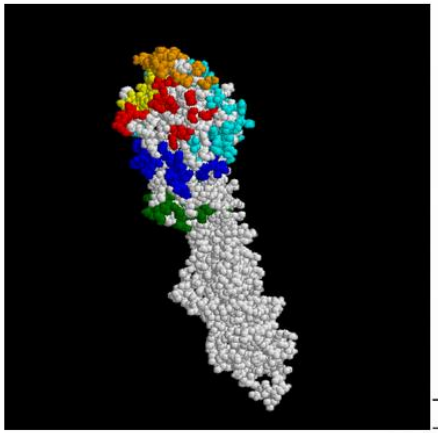
- **Time-consuming (6-9 months)**
  - Recombinant HA protein vaccines
- **Egg-based vaccine**
  - Allergies
  - Shortages (pandemic)
  - Novartis = cell-based (MDCK) vaccines
- **Bacterial contamination**
- **Inability to grow in eggs**
- **Mismatch from circulating strains**
  - Constant surveillance (WHO = 1952)
- **Immunogenicity**
  - MF59 adjuvant

Future Varieties of Influenza Vaccines?

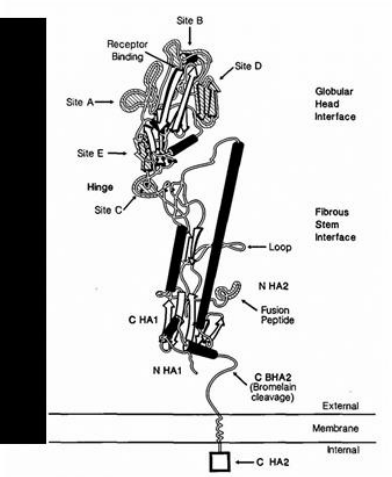
- **Neuraminidase**
- **Conserved epitopes**
  - HA stem (less variability)
  - M2e (23 conserved amino acids)



Antigenic Site A
Antigenic Site B
Antigenic Site C
Antigenic Site D
Antigenic Site E
Receptor Binding



A/Hong Kong/1/68 HA

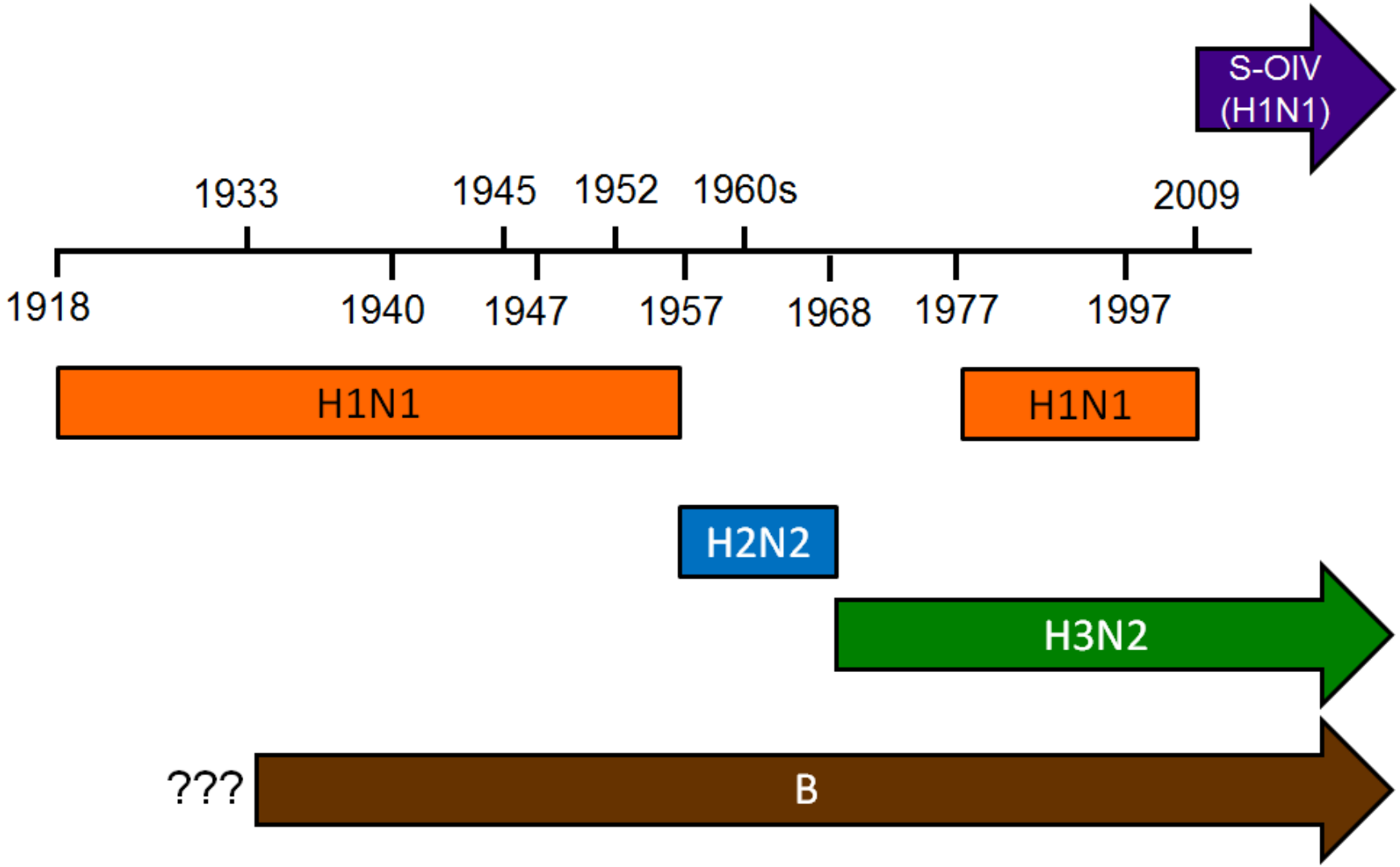


Fields Virology

Summary

- Surveillance identifies genetic and antigenic changes in influenza viruses
- Vaccination remains our best tool for preventing infection
- Current vaccines come in IIV, LAIV, and recombinant HA forms
- Not all issues have been resolved, and future vaccines are being developed to provide more universal immunity

Questions?


S-OIV
(H1N1)
1933
1945
1952
1960s
2009
1918
1940
1947
1957
1968
1977
1997
H1N1
H1N1
H2N2
H3N2
???
B